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(54) Pharmaceutical composition

(57) A water-swellable, water-insoluble polymer is loaded with a biologically active substance or substance which is converted thereinto *in vivo*, for example a drug or pro-drug, by preparing a mixture of a said substance with a thermally stable water-swellable, water-insoluble polymer in a weight ratio of the said substance: polymer of from 1:0.1 to 1:100 and heating said mixture up to the melting temperature of the said substance. The thus-loaded polymer is useful as a pharmaceutical composition.

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SPECIFICATION

Pharmaceutical composition

This invention relates to the preparation of formulations comprising a biologically active substance or substance which is converted thereinto *in vivo*.

The wettability and dissolution properties of a biologically active substance or substance which is converted thereinto *in vivo* such as a drug or pro-drug greatly influence its bioavailability. In many cases very active drugs or pro-drugs, for example, present a poor absorption profile due to their unfavourable dissolution characteristics. Reduction of their particle size and addition of wetting agents, widely applied to overcome these problems, very frequently prove to be not effective enough. Therefore much effort has been devoted to develop new formulations or new techniques to get better results. Considerable attention have recently gained two new research lines based on the preparation of "solid dispersions" and of "inclusion compounds". In the former approach the drug or pro-drug is molecularly dispersed in the carrier, usually a water-soluble polymer (S. Riegelman, W.L. Chiou 987,588 4/1976 Canada), while in the latter the drug or pro-drug forms molecular complexes with water-soluble cyclodextrins (J. Szejtli "Cyclodextrins and their inclusion compounds", Akademia Viado, Budapest 1982).

A remarkable enhancement of the dissolution and bioavailability of poorly water-soluble substances can be also achieved by the procedure of the present invention in which a biologically active substance or substance converted thereinto *in vivo* is loaded in/on swellable, water-insoluble polymers by heating up to the melting temperature of the substance mixtures of substances and said polymers. Specifically, if a drug or pro-drug has physico-chemical characteristics which are unfavourable (poor wettability, poor dissolution characteristics in aqueous media) to its *in vivo* absorption, heating a mixture of it and a swellable water-insoluble polymer improves these characteristics and consequently can bring about an enhanced bioavailability.

This is due to one or both the following effects brought about by the heating process:

1. Increase of wettability of the drug or pro-drug as consequence of the very large dispersion of it in/on the network of the highly hydrophylic and swellable polymer.

2. Increase of solubility caused by a complete or partial transition of the original crystalline network of the drug or pro-drug to a higher energy (lower melting point) structure and/or to a completely or partially amorphous form.

In addition to the above specified advantages, the drug or pro-drug loaded on the aforementioned polymers may also present other improved chemico-physical or technological properties.

Accordingly, the present invention provides a process for loading a water-swellable water-insoluble polymer with a biologically active substance or substance which is converted thereinto *in vivo*, which process comprises (i) preparing a mixture of a said substance with a water-swellable water-insoluble polymer which is stable under the heating to which the mixture is subjected in step (ii) in a weight ratio of the said substance: polymer of from 1:0.1 to 1:100 and (iii) heating said mixture up to the melting temperature of the said substance.

The present invention also provides a water-swellable, water-insoluble polymer which has been loaded with a biologically active substance or substance which is converted thereinto *in vivo* in a weight ratio of the said substance:polymer of from 1:0.1 to 1:100 by the process of the invention.

The biologically active substance or substance which is converted thereinto *in vivo* is preferably a drug or pro-drug. For convenience hereinafter drugs and pro-drugs will be referred to collectively as "drugs", with reference to which the present invention will be described by way of example below.

The basic advantages of the drug polymer systems obtained according to the present invention are:

1. Remarkable increase of the drug wettability due to the high hydrophilicity and swelling capacity in water of the hydrophilic, swellable, water-insoluble polymers.

2. Rapid swelling and disintegration in water of the system and immediate dispersion of the drug. Some of the hydrophilic, swellable, water-insoluble polymers which may be used in the present process are in fact already used and marketed as disintegrants for oral solid dosage forms.

3. Avoidance of the viscous layer around the drug which can be related with the use of water-soluble polymers and which can hinder the drug diffusion and slow down the dissolution process.

In addition, loading of drugs in/on swellable water-insoluble polymers by the coheating technique presents advantages over the loading method based on swelling of the polymer in an organic solvent containing the drug (B.C. Lippold et al., D.O.S., 2,634,004). The basic advantages of the coheating technique over the swelling method are:

1. The avoidance of all the problems of toxicity and inflammability related to the use of solvents.

2. The possibility of loading larger quantities of drug on/in the swellable polymer; in fact the maximum amount of drug which can be loaded by the solvent swelling method is limited both by the swelling volume and the solubility of the drug in that solvent.

3. At low drug/swellable polymer ratio, better dissolution and consequently also better bioavailability can be achieved by the heated mixture compared to the solvent loaded mixture, as the heating technique can lead about higher degree of amorphization.

This invention is concerned with the heating up to the melting temperature of the drug of a mixture of an

active drug and any water-insoluble, hydrophylic, swellable polymer (or combination of two or more thereof). Non-limiting examples of such polymers are:

a) crosslinked PVP (National Formulary XV, Supplement 3, page. 368), hereafter shortened in crosslinked PVP;

b) crosslinked sodium carboxymethylcellulose (National Formulary XV, Supplement 3, page 365);

c) crosslinked dextran etc.

The common characteristics of these polymers are:

1. High swelling ability in water (from 0.1 ml to 100 ml of water volume uptake per gram of drug polymer). This characteristic brings about a high swelling and an effective disintegration (in water or in biological fluids) of the systems with a powerful dispersion of its constituents and an immediate release of the drug molecules.

2. Fast rate of water swelling (e.g. crosslinked PVP achieves maximum swelling in less than five minutes). This property allows that the aforementioned effects of swelling, disintegration, dispersion and dissolution of the drug molecules are accomplished in a very short period of time.

3. Water insolubility. This property rules out possible negative effects able to slow down the drug dissolution process, e.g. by building up a viscous layer around the drug, and brings about the formation of a finely dispersed suspension which assures a rapid gastric emptying to the absorption site.

4. No degradation or melting up to the melting temperature of the drug. In other words, the polymer must be thermally stable under the heating to which it is subjected. This means, for example, that crosslinked PVP, which, in a controlled atmosphere, does not present any detectable degradation up to 300°C, can be used for the treatment of drugs with high melting temperatures; on the contrary, crosslinked dextran (caramelization temperature 120°C) can be used only with drugs with melting temperatures below 120°C; etc.

The basic procedure of the heating technique of a mixture of an active drug and any (or combinations thereof) water-insoluble, swellable, hydrophylic polymer to which this invention relates, can be detailed as follows:

A dry mixture of the drug and any of the swellable insoluble polymers aforementioned (chosen among those with good thermal stability at the melting point of the drug) is placed in a container inside a thermoregulated high vacuum oven; after evacuation a nitrogen flow is established over the drug-polymer mixture and temperature raised to a value higher than the melting point of the drug. Alternatively the mixture of the drug and the polymer is placed in the glass flask of a rotating evaporator; after evacuation, a flow of nitrogen is established over the drug-polymer mixture and the glass flask placed in an oil bath at a temperature higher than the melting point of the drug. Any other heating apparatus (hot plate, muffle, tube oven etc.) can be usefully applied, as long as the temperature can be carefully checked and held constant. In any case the temperature must be raised to a value sufficient to ensure the melting of the drug.

The drug-polymer mixture is heated as long as the desired degree of amorphization of the drug is achieved, which can be checked by Differential Scanning Calorimetry. In fact the absence in the thermogram of the peak relative to the solid/liquid transition of the crystalline drug means the product is completely amorphous (enthalpy of melting equal to zero). Obviously the heating process can be also stopped any time a degree (0-100%) of amorphization (measured by the reduction of the melting enthalpy) sufficient to sensibly increase the dissolution rate is achieved. Alternatively, the heating process can be stopped any time the original crystalline form of the drug has been transformed into another, more energetic form (this transformation is indicated by the shifting of the original endothermic peak to lower temperatures), leading to higher dissolution rate and bioavailability.

Weight ratios of drug and the polymer in the mixture to be heated can vary from 1:0.1 to 1:100 w.w. drug: polymer, preferably from 1:1 to 1:100 w.w. drug:polymer. For each drug: polymer weight ratio composition and each total amount of mixture, the time of heating necessary to achieve the desired degree of amorphization must be checked; therefore for each drug-polymer system the most practical combination of weight ratio and time of heating can be identified.

Examples of drug: polymer weight ratio compositions, of heating temperature and time will be given later.

The resulting heated mixture of the active drug and the swellable insoluble polymer can then be forced through a sieve to eliminate possible aggregates and subsequently mixed in any mixing device to warrant further homogeneity. The resulting powdered heated system of the drug and the swellable polymer can be subsequently used to prepare any desired dosage form (e.g., capsules, tablets etc.) with or without the addition of any of the common excipients used in pharmaceutical formulations. Any active drug with poor dissolution characteristics can be treated by the swellable polymer coheating technique described by this invention. Non limiting examples of classes of drugs are: slightly soluble steroid hormones; non-steroidal hormones; antibiotics; antiinflammatory drugs; sedative drugs; etc. The amount of the polymer/drug system of the invention which is administered to a subject will depend upon a variety of factors including the drug employed, the condition to be treated and the age and condition of the patient.

The following non-limiting examples illustrate methods of making the preparations of the present invention.

Example 1

0.15 gram of crystalline methylhydroxyprogesterone acetate (MAP) and 0.75 gram of crosslinked PVP were mixed with a suitable mixing apparatus, subsequently placed in the glass flask of a rotating evaporator and heated in an oil bath at 216°C for 45 minutes, under nitrogen flow. The resulting MAP / crosslinked PVP

SPECIFICATION

Pharmaceutical composition

This invention relates to the preparation of formulations comprising a biologically active substance or substance which is converted thereinto *in vivo*.

The wettability and dissolution properties of a biologically active substance or substance which is converted thereinto *in vivo* such as a drug or pro-drug greatly influence its bioavailability. In many cases very active drugs or pro-drugs, for example, present a poor absorption profile due to their unfavourable dissolution characteristics. Reduction of their particle size and addition of wetting agents, widely applied to overcome these problems, very frequently prove to be not effective enough. Therefore much effort has been devoted to develop new formulations or new techniques to get better results. Considerable attention have recently gained two new research lines based on the preparation of "solid dispersions" and of "inclusion compounds". In the former approach the drug or pro-drug is molecularly dispersed in the carrier, usually a water-soluble polymer (S. Riegelman, W.L. Chiou 987,588 4/1976 Canada), while in the latter the drug or pro-drug forms molecular complexes with water-soluble cyclodextrins (J. Szejtli "Cyclodextrins and their inclusion compounds", Akademia Viado, Budapest 1982).

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This is due to one or both the following effects brought about by the heating process:

1. Increase of wettability of the drug or pro-drug as consequence of the very large dispersion of it in/on the network of the highly hydrophylic and swellable polymer.

2. Increase of solubility caused by a complete or partial transition of the original crystalline network of the drug or pro-drug to a higher energy (lower melting point) structure and/or to a completely or partially amorphous form.

In addition to the above specified advantages, the drug or pro-drug loaded on the aforementioned polymers may also present other improved chemico-physical or technological properties.

Accordingly, the present invention provides a process for loading a water-swellable water-insoluble polymer with a biologically active substance or substance which is converted thereinto *in vivo*, which process comprises (i) preparing a mixture of a said substance with a water-swellable water-insoluble polymer which is stable under the heating to which the mixture is subjected in step (ii) in a weight ratio of the said substance: polymer of from 1:0.1 to 1:100 and (iii) heating said mixture up to the melting temperature of the said substance.

The present invention also provides a water-swellable, water-insoluble polymer which has been loaded with a biologically active substance or substance which is converted thereinto *in vivo* in a weight ratio of the said substance:polymer of from 1:0.1 to 1:100 by the process of the invention.

The biologically active substance or substance which is converted thereinto *in vivo* is preferably a drug or pro-drug. For convenience hereinafter drugs and pro-drugs will be referred to collectively as "drugs", with reference to which the present invention will be described by way of example below.

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3. Avoidance of the viscous layer around the drug which can be related with the use of water-soluble polymers and which can hinder the drug diffusion and slow down the dissolution process.

In addition, loading of drugs in/on swellable water-insoluble polymers by the coheating technique presents advantages over the loading method based on swelling of the polymer in an organic solvent containing the drug (B.C. Lippold et al., D.O.S., 2,634,004). The basic advantages of the coheating technique over the swelling method are:

1. The avoidance of all the problems of toxicity and inflammability related to the use of solvents.

2. The possibility of loading larger quantities of drug on/in the swellable polymer; in fact the maximum amount of drug which can be loaded by the solvent swelling method is limited both by the swelling volume and the solubility of the drug in that solvent.

3. At low drug/swellable polymer ratio, better dissolution and consequently also better bioavailability can be achieved by the heated mixture compared to the solvent loaded mixture, as the heating technique can lead about higher degree of amorphization.

This invention is concerned with the heating up to the melting temperature of the drug of a mixture of an

active drug and any water-insoluble, hydrophylic, swellable polymer (or combination of two or more thereof). Non-limiting examples of such polymers are:

a) crosslinked PVP (National Formulary XV, Supplement 3, page. 368), hereafter shortened in crosslinked PVP;

b) crosslinked sodium carboxymethylcellulose (National Formulary XV, Supplement 3, page 365);

c) crosslinked dextran etc.

The common characteristics of these polymers are:

1. High swelling ability in water (from 0.1 ml to 100 ml of water volume uptake per gram of drug polymer). This characteristic brings about a high swelling and an effective disintegration (in water or in biological fluids) of the systems with a powerful dispersion of its constituents and an immediate release of the drug molecules.

2. Fast rate of water swelling (e.g. crosslinked PVP achieves maximum swelling in less than five minutes). This property allows that the aforementioned effects of swelling, disintegration, dispersion and dissolution of the drug molecules are accomplished in a very short period of time.

3. Water insolubility. This property rules out possible negative effects able to slow down the drug dissolution process, e.g. by building up a viscous layer around the drug, and brings about the formation of a finely dispersed suspension which assures a rapid gastric emptying to the absorption site.

4. No degradation or melting up to the melting temperature of the drug. In other words, the polymer must be thermally stable under the heating to which it is subjected. This means, for example, that crosslinked PVP, which, in a controlled atmosphere, does not present any detectable degradation up to 300°C, can be used for the treatment of drugs with high melting temperatures; on the contrary, crosslinked dextran (caramelization temperature 120°C) can be used only with drugs with melting temperatures below 120°C; etc.

The basic procedure of the heating technique of a mixture of an active drug and any (or combinations thereof) water-insoluble, swellable, hydrophylic polymer to which this invention relates, can be detailed as follows:

A dry mixture of the drug and any of the swellable insoluble polymers aforementioned (chosen among those with good thermal stability at the melting point of the drug) is placed in a container inside a thermoregulated high vacuum oven; after evacuation a nitrogen flow is established over the drug-polymer mixture and temperature raised to a value higher than the melting point of the drug. Alternatively the mixture of the drug and the polymer is placed in the glass flask of a rotating evaporator; after evacuation, a flow of nitrogen is established over the drug-polymer mixture and the glass flask placed in an oil bath at a temperature higher than the melting point of the drug. Any other heating apparatus (hot plate, muffle, tube oven etc.) can be usefully applied, as long as the temperature can be carefully checked and held constant. In any case the temperature must be raised to a value sufficient to ensure the melting of the drug.

The drug-polymer mixture is heated as long as the desired degree of amorphization of the drug is achieved, which can be checked by Differential Scanning Calorimetry. In fact the absence in the thermogram of the peak relative to the solid/liquid transition of the crystalline drug means the product is completely amorphous (enthalpy of melting equal to zero). Obviously the heating process can be also stopped any time a degree (0-100%) of amorphization (measured by the reduction of the melting enthalpy) sufficient to sensibly increase the dissolution rate is achieved. Alternatively, the heating process can be stopped any time the original crystalline form of the drug has been transformed into another, more energetic form (this transformation is indicated by the shifting of the original endothermic peak to lower temperatures), leading to higher dissolution rate and bioavailability.

Weight ratios of drug and the polymer in the mixture to be heated can vary from 1:0.1 to 1:100 w.w. drug: polymer, preferably from 1:1 to 1:100 w.w. drug:polymer. For each drug: polymer weight ratio composition and each total amount of mixture, the time of heating necessary to achieve the desired degree of amorphization must be checked; therefore for each drug-polymer system the most practical combination of weight ratio and time of heating can be identified.

Examples of drug: polymer weight ratio compositions, of heating temperature and time will be given later.

The resulting heated mixture of the active drug and the swellable insoluble polymer can then be forced through a sieve to eliminate possible aggregates and subsequently mixed in any mixing device to warrant further homogeneity. The resulting powdered heated system of the drug and the swellable polymer can be subsequently used to prepare any desired dosage form (e.g., capsules, tablets etc.) with or without the addition of any of the common excipients used in pharmaceutical formulations. Any active drug with poor dissolution characteristics can be treated by the swellable polymer coheating technique described by this invention. Non limiting examples of classes of drugs are: slightly soluble steroid hormones; non-steroidal hormones; antibiotics; antiinflammatory drugs; sedative drugs; etc. The amount of the polymer/drug system of the invention which is administered to a subject will depend upon a variety of factors including the drug employed, the condition to be treated and the age and condition of the patient.

The following non-limiting examples illustrate methods of making the preparations of the present invention.

Example 1

0.15 gram of crystalline methylhydroxyprogesterone acetate (MAP) and 0.75 gram of crosslinked PVP were mixed with a suitable mixing apparatus, subsequently placed in the glass flask of a rotating evaporator and heated in an oil bath at 216°C for 45 minutes, under nitrogen flow. The resulting MAP / crosslinked PVP

system was then sieved to 260 μm and mixed with a suitable mixing apparatus. This powdered system could then be incorporated in any desired solid dosage form.

Example 2

0.15 gram of crystalline indoprofen and 0.45 gram of crosslinked PVP were mixed with a suitable mixing apparatus, subsequently placed in the glass flask of a rotating evaporator and heated in an oil bath at 225°C for 30 minutes, under vacuum. The resulting indoprofen / crosslinked PVP system was then sieved to 260 μm and mixed with a suitable mixing apparatus. This powdered system could then be incorporated in any desired solid dosage form.

Example 3

0.25 gram of crystalline indoprofen and 0.25 gram of crosslinked PVP were mixed with a suitable mixing apparatus, subsequently placed in the glass flask of a rotating evaporator and heated in an oil bath at 220°C for 30 minutes, under vacuum. The resulting indoprofen / crosslinked PVP system was then sieved to 260 μm and mixed with a suitable mixing apparatus. This powdered system could then be incorporated in any desired solid dosage form.

Example 4

0.3 gram of crystalline griseofulvin and 0.9 gram of crosslinked PVP were mixed with a suitable mixing apparatus, subsequently placed in the glass flask of a rotating evaporator and heated in an oil bath at 235°C, for 20 minutes, under nitrogen flow. The resulting griseofulvin/crosslinked PVP system was then sieved to 260 μm and mixed with a suitable mixing apparatus. This powdered system could then be incorporated in any desired solid dosage form.

Example 5

0.15 gram of crystalline griseofulvin and 0.45 gram of crosslinked PVP were mixed with a suitable mixing apparatus, subsequently placed in the glass flask of a rotating evaporator and heated in an oil bath at 235°C, for 45 minutes, under nitrogen flow. The resulting griseofulvin/crosslinked PVP system was then sieved to 260 μm and mixed with a suitable mixing apparatus. This powdered system could then be incorporated in any desired solid dosage form.

Example 6

0.1 gram of crystalline griseofulvin and 0.5 gram of crosslinked PVP were mixed with a suitable mixing apparatus, subsequently placed in the glass flask of a rotating evaporator and heated in an oil bath at 235°C, for 45 minutes, under vacuum. The resulting griseofulvin/crosslinked PVP system was then sieved to 260 μm and mixed with a suitable mixing apparatus. This powdered system could then be incorporated in any desired solid dosage form.

Example 7

0.3 gram of crystalline indomethacin and 0.9 gram of crosslinked PVP were mixed with a suitable mixing apparatus, subsequently placed in the glass flask of a rotating evaporator and heated in an oil bath at 175°C, for 45 minutes under nitrogen flow. The resulting indomethacin/crosslinked PVP system was then sieved to 260 μm and mixed with a suitable mixing apparatus. This powdered system could then be incorporated in any desired solid dosage form.

Example 8

0.1 gram of crystalline indomethacin and 0.5 gram of crosslinked PVP were mixed with a suitable mixing apparatus, subsequently placed in the glass flask of a rotating evaporator and heated in an oil bath at 175°C, for 45 minutes, under nitrogen flow. The resulting indomethacin/crosslinked PVP system was then sieved to 260 μm and mixed with a suitable mixing apparatus. This powdered system could then be incorporated in any desired solid dosage form.

Example 9

0.3 gram of crystalline indomethacin and 0.9 gram of crosslinked sodium carboxymethylcellulose were mixed with a suitable mixing apparatus, subsequently placed in the glass flask of a rotating evaporator and heated in an oil bath at 175°C, for 45 minutes, under nitrogen flow. The resulting indomethacin/crosslinked sodium carboxymethylcellulose system was then sieved to 260 μm and mixed with a suitable mixing apparatus. This powdered system could then be incorporated in any desired solid dosage form.

Differential scanning calorimetry data

The D.S.C. (TA 3000, Mettler) data relative to the preparation by heating containing MAP described in example 1, are presented in Table 1 : after 45 minutes of heating at 216°C the mixture MAP : crosslinked PVP 1:5 w/w presents a complete amorphization (no residual crystallinity) of MAP.

As shown in Table 2, both with a mixture 1:1 w/w Indoprofen : PVP crosslinked and a mixture 1:3 w/w, after 30 minutes at 225°C or at 220°C a complete amorphization is achieved.

In the case of the griseofulvin heated systems, as shown in Table 3, the heating for 20 minutes at 235°C of a 1:3 w/w griseofulvin : crosslinked PVP mixture leads to a ~90% reduction of the original heat of fusion and to a parallel shifting of the melting point to a lower value. A complete amorphization is achieved, both for the 1:3 and 1:5 w/w mixtures, after 45 minutes of heating at 235°C.

As shown in Table 4, mixtures of Indomethacin and crosslinked PVP, both at 1:3 and 1:5 weight ratios, after heating at 175°C for 45 minutes, present a ~90% reduction of the original heat of fusion, whereas the mixture with crosslinked sodium carboxymethylcellulose, at 1:5 w/w ratio, at the same time of heating, leads about a complete amorphization.

Solubility data

A) MAP/swellable polymer heated mixture

The solubility of the MAP/swellable polymer heated mixture described in Example 1 was assessed by placing an excess amount of the powder, equivalent to 50 mg of MAP, in flasks containing 50 ml of pH 5.5 buffer solution, at 37°C; the flasks were placed in a shaking thermostated apparatus and aliquots of sample solution were taken by filtering through a Millipore membrane; concentration of MAP in the filtered aliquot was determined both by spectrophotometry (SP8-100 Pye Unicam), at λ =247 nm, after dilution with methanol, and by HPLC (column: Spherisorb S30 D52, Phase Sep.; mobile phase: acetonitrile/water 70/30 v/v; flow rate : 1 ml/min; U.V. detection; λ =242nm), after dilution with acetonitrile.

The solubility data of the MAP/crosslinked PVP 1:5 w/w heated mixture described in Example 1 are reported in Table 5. It is possible to observe that the heated mixture prepared by the technique described by this invention originates MAP concentrations higher than the pure MAP or the physical mixture of MAP and crosslinked PVP. Even more important is to observe that the heated mixture proves to have a better solubility pattern than the MAP/crosslinked PVP 1:5 w/w system prepared by the solvent swelling technique (4 ml of 50.0 mg/ml methylenechloride solution of MAP over 1 g of crosslinked PVP).

B) Indoprofen/swellable polymer heated mixtures

The solubility of the Indoprofen/crosslinked PVP heated mixtures described in Examples 2 and 3 was measured by following the procedure used for the MAP systems and a pH 2.0 buffer solution; the Indoprofen concentrations were determined by spectrophotometry (λ =280 nm).

As shown in Table 6, both the Indoprofen/crosslinked PVP 1:1 and 1:3 w/w heated mixtures originate Indoprofen concentrations higher than in the case of the pure drug and of the physical mixture of the drug and the crosslinked PVP. Furthermore the heated mixtures originate Indoprofen concentrations as high as the Indoprofen/crosslinked PVP 1:4 w/w system prepared by the solvent swelling method (2.5 ml of 100 mg/ml dimethylformamide solution of Indoprofen over 1 g of crosslinked PVP), but it is important to stress that these concentrations are obtained at drug : polymer ratios (1:1 and 1:3 w/w) lower than the most favourable ratio which could be obtained by the solvent swelling method (1:4 w/w).

C) Griseofulvin/swellable polymer heated mixtures

The solubility of the Grisefulvin/crosslinked PVP heated mixtures described in Examples 4, 5 and 6 was measured by the following the procedure used for the MAP systems and a pH 7.5 buffer solution; the Grisefulvin concentrations were determined by spectrophotometry (λ= 294 nm).

As shown in Table 7, the Griseofulvin/crosslinked PVP heated mixtures originate drug concentrations very much higher than the pure Griseofulvin or the physical mixture of Griseofulvin and crosslinked PVP. Furthermore, also the drug concentrations originated by the system prepared by the solvent swelling technique (4 ml of 83.3 mg/ml dimethylformamide solution of Griseofulvin over 1 gram of crosslinked PVP) are very much lower than the concentrations originated by the heated mixtures.

D) Indomethacin/swellable polymer heated mixtures

The solubility of the Indomethacin/crosslinked PVP heated mixtures described in Examples 7, 8 and 9 was measured by following the procedure used for the MAP systems and a pH 6.8 buffer solution; the Indomethacin concentrations were determined by spectrophotometry (λ = 317 nm).

As shown in Table 8, the Indomethacin concentrations originated at shorter times by the heated mixtures, both containing crosslinked PVP and crosslinked Sodium Carboxymethylcellulose, are higher than the concentrations given by the pure drug and the physical mixture drug/crosslinked PVP. Furthermore, Indomethacin concentrations originated by the heated mixtures are as high as those obtained by the solvent swelling technique (4 ml of 50.0 mg/ml acetone solution of Indomethacin over 1 gram of crosslinked PVP), but these concentrations are also obtained at drug : polymer ratios (1:3) lower than the most favourable ratio which could be obtained by the solvent swelling method (1:5 w/w).

On the basis of the previously shown solubility data, it is possible to conclude that the drug/swellable water insoluble polymer systems prepared by the heating technique described by this invention possess the property to increase the solubilization characteristics of the drugs. In fact solubility values not only higher than those obtained by the corresponding polymer/drug physical mixtures can be achieved but also higher than those originated by drug/swellable water-insoluble polymer systems prepared by the solvent swelling technique. Anyway, it was evidentiated that also when the systems prepared by the heating technique

originated drug solubility data as high as the concentrations obtained by the solvent swelling systems, these concentrations were achieved at more favourable drug : polymer ratio, i.e. using less polymer.

TABLE 1

Differential Scanning Calorimetry Data of Methylhydroxyprogesterone acetate (MAP) /Swellable Polymer Heated Mixture.

System	*Melting Point °C*	*Heat of Fusion J/g*	*% Residual of Original Heat of Fusion*
Pure crystalline MAP	205-206	88.0	100
MAP/crosslinked PVP 1:5w/w (heating method, 45 min at 216°C) Example 1	-	-	0

TABLE 2

Differential Scanning Calorimetry Data of Indoprofen/Swellable Polymer Heated Mixtures.

System	*Melting Point °C*	*Heat of Fusion J/g*	*% Residual of Original Heat of Fusion*
Pure crystalline Indoprofen	212-215	134.6	100.00
Indoprofen/crosslinked PVP 1:1w/w (heating method 30 min at 220°C) Example 3	-	0	0
Indoprofen/crosslinked PVP 1:3w/w (heating method 30 min at 225°C) Example 2	-	0	0

TABLE 3

Differential Scanning Calorimetry Data of Griseofulvin/Swellable Polymer Heated Mixtures.

System	*Melting Point °C*	*Heat of Fusion J/g*	*% Residual of Original Heat of Fusion*
Pure crystalline Griseofulvin	218.8	119.2	100
Griseofulvin/crosslinked PVP 1:3w/w (heating method, 20 min at 235°C) Example 4	202.7	10.4	8.7
Griseofulvin/crosslinked PVP 1:3w/w (heating method, 45 min at 235°C) Example 5	-	0	0
Griseofulvin/crosslinked PVP 1:5w/w (heating method, 45 min at 235°C) Example 6	-	0	0

TABLE 4

Differential Scanning Calorimetry Data of Indomethacin/Swellable Polymer Heated Mixtures.

System	*Melting Point °C*	*Heat of Fusion J/g*	*% Residual of Original Heat of Fusion*
Pure crystalline Indomethacin	160.2	110.8	100
Indomethacin/crosslinked PVP 1:3w/w (heating method, 45 min at 175°C) Example 7	160.2	9.7	8.6
Indomethacin/crosslinked PVP 1:5w/w (heating method, 45 min at 175°C) Example 8	160.6	11.3	10.9
Indomethacin/crosslinked Sodium Carboxymethylcellulose 1:3w/w (heating method, 45 min at 175°C) Example 9	-	0	0

TABLE 5

Solubility Data (mcg/ml) of Methylhydorxyprogesterone acetate (MAP)/Swellable Polymer Heated Mixture (pH 5.5 phosphate buffer, 37°C)

	Time			
System	*5 min*	*15 min*	*1 hr*	*6 hrs*
Pure crystalline MAP	<0.04	0.32	0.68	1.00
Physical Mixture 1:3 w/w MAP/crosslinked PVP	0.85	1.18	1.34	1.21
MAP/crosslinked PVP 1:5w/w (heating method, 45 min at 216°C) Example 1	3.83	6.10	4.76	3.28
MAP/crosslinked PVP 1:5w/w (solvent swelling method)	1.00	1.61	1.69	2.04

TABLE 6

Solubility Data (mcg/ml) of Indoprofen/Swellable Polymer Heated Mixtures (pH 1.2 buffer solution, 37°C)

System	*Time* 5 min	15 min	1 hr	3 hrs	24 hrs
Pure crystalline Indoprofen	1.6	3.0	4.8		10.3
Physical Mixture 1:3 w/w Indoprofen/crosslinked PVP	8.3	8.2	9.6	10.2	11.3
Indoprofen/crosslinked PVP 1:3 w/w (heating method, 30 min at 225°C) Example 2	13.9	19.1	19.1	19.2	-
Indoprofen/crosslinked PVP 1:1 w/w (heating method, 30 min at 220°C) Example 3	12.9	14.0	17.0	17.0	-
Indoprofen/crosslinked PVP 1:4 w/w (solvent swelling method)	19.3	16.8	15.7	14.6	14.8

TABLE 7

Solubility Data (mcg/ml) of Griseofulvin/Swellable Polymer Heated Mixtures (pH 7.4 buffer solution, 37°C)

System	*Time* 5 min	15 min	1 hr	3 hrs	24 hrs
Pure crystalline Griseofulvin	9.1	11.0	10.9	11.3	14.9
Physical Mixture 1:3 w/w Griseofulvin/crosslinked PVP	18.9	19.3	21.2	23.9	-
Griseofulvin/crosslinked PVP 1:3w/w (heating method 20 min at 235°C) Example 4	64.8	62.8	66.5	65.5	60.9
Griseofulvin/crosslinked PVP 1:3 w/w (heating method 45 min at 235°C) Example 5	88.5	95.2	100.6	98.7	96.3
Griseofulvin/crosslinked PVP 1:5 w/w (heating method 45 min at 235°C) Example 6	107.1	87.5	81.2	80.6	-
Griseofulvin/crosslinked PVP 1:3 w/w (solvent swelling method)	24.7	24.2	24.0	19.9	19.1

TABLE 8

Solubility Data (mcg/ml) of Indomethacin/Swellable Polymer Heated Mixtures (pH 6.8 buffer solution, 37°C)

System	*Time*				
	5 min	*15 min*	*1 hr*	*3 hrs*	*24 hrs*
Pure crystalline Indomethacin	230.2	358.2	482.1	502.8	502.0
Physical Mixture Indomethacin/crosslinked PVP 1:5 w/w	184.7	264.3	364.3	389.6	522.5
Indomethacin/crosslinked PVP 1:5 w/w (heating method 45 min at 175°C) Example 8	489.1	515.4	499.0	502.5	-
Indomethacin/crosslinked PVP 1:3 w/w (heating method 45 min at 175°C) Example 7	473.1	484.1	485.3	483.1	-
Indomethacin/crosslinked Sodium Carboxymethylcellulose 1:3 w/w (heating method, 45 min at 175°C) Example 9	418.6	473.4	481.5	480.1	484.3
Indomethacin/crosslinked PVP 1:5 w/w (solvent swelling method)	464.6	475.5	475.4	489.6	496.0

CLAIMS

1. A process for loading a water-swellable water-insoluble polymer with a biologically active substance or substance which is converted thereinto *in vivo*, which process comprises (i) preparing a mixture of a said substance with a water-swellable water-insoluble polymer which is stable under the heating to which the mixture is subjected in step (ii) in a weight ratio of the said substance:polymer of from 1:0.1 to 1:100 and (iii) heating said mixture up to the melting temperature of the said substance.

2. A process according to claim 1 in which the said substance is a drug or pro-drug.

3. A process according to claim 1 or 2 in which said polymer is cross-linked polyvinylpyrrolidone or cross-linked sodium carboxymethylcellulose.

4. A process according to any one of the preceding claims in which two or more water-swellable, water-insoluble polymers are employed in step (i).

5. A water-swellable, water-insoluble polymer which has been loaded with a biologically active substance or substance which is converted thereinto *in vivo* in a weight ratio of the said substance:polymer of from 1:0.1 to 1:100 by a process as claimed in any one of the preceding claims.

6. A pharmaceutical composition comprising a water-swellable, water-insoluble polymer loaded with a biologically active substance or substance which is converted thereinto *in vivo* which has been prepared by a process as claimed in any one of claims 1 to 4 or which is as claimed in claim 5.

7. A composition according to claim 6 further comprising a pharmaceutically acceptable excipient.

8. A process for loading a water-swellable, water-insoluble polymer with a biologically active substance or substance which is converted thereinto *in vivo*, said process being substantially as hereinbefore described in any one of Examples 1 to 9.

9. A water-swellable, water-insoluble polymer loaded with a biologically active substance or substance which is converted thereinto *in vivo*, said loaded polymer being substantially as hereinbefore described in any one of Examples 1 to 9.

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